

## Review

## Systemic gonococcal infection

J D C Ross

During this century changes in sexual behaviour in the Western world in conjunction with the development of effective antimicrobial therapy have resulted in wide ranging peaks and troughs in the incidence of many sexually transmitted diseases. Following the introduction of penicillin in the post war years gonorrhoea, in particular, almost disappeared only to rise again during the "sexual revolution" of the 1960s. After a peak in the late 1970s there occurred a dramatic fall in incidence of the same proportion seen after the introduction of penicillin, largely as a result of public concern about the risks of contracting HIV. Disseminated gonococcal infection (DGI) occurs in 0.2%–1.9% of cases of mucosal infection<sup>1,2</sup> and it is therefore not surprising that it has declined almost to the point of extinction in many areas. Despite the present rarity of the condition it remains an important cause of morbidity and occasionally mortality in the young sexually active population. As recently as the early 1980s the commonest reason for admission with infective arthritis in the USA was DGI<sup>3,4</sup> estimated at 2.8 cases per 100 000 per year. With recent reports suggesting that the declining incidence of gonorrhoea has plateaued and may be rising in some groups such as gay men,<sup>5-7</sup> and the continuing high levels of disease which persist in many developing countries,<sup>8-10</sup> DGI remains an important condition to recognise promptly and treat appropriately.

**Who gets DGI?**

Although the earliest reports of disseminated gonorrhoea suggested that men were more likely to be infected,<sup>11</sup> the more recent literature estimates a male to female ratio of around 1:4.<sup>3,4,12-14</sup> Pregnancy and the peri-menstrual interval may further increase the risk of DGI in women as a result of associated changes in gonococcal phenotype from opaque to transparent (which is more resistant to the killing action of normal serum) in conjunction with alterations in vaginal pH, cervical mucous and the genital flora.<sup>14-17</sup> The asymptomatic nature of many female infections may also give more opportunity for systemic spread to occur but although gay men are also infected at sites which are asymptomatic they do not appear to be at increased risk. Both the age range of those affected and their ethnic background appear to mirror those of uncomplicated gonorrhoea for individual areas.<sup>18,19</sup> The role of immunosuppression secondary to alcoholism, steroids, IV drug misuse, systemic lupus erythematosus and complement deficiency syndromes is unclear but probably contributes to a

small number of cases, particularly in those with recurrent episodes of DGI.<sup>12</sup>

**What kind of gonococci cause systemic infection?**

There is some evidence that the risk of dissemination is dependant not just on the ability of the patient's immune system to control the infection, but that particular subtypes of *N gonorrhoeae* may be more likely to be invasive than others.<sup>20</sup> Gonococci which lack Protein II in their outer membrane may have an impaired chemotactic response and are associated with DGI, as are strains of the AHU<sup>-</sup> auxotype and Protein IA serotype.<sup>3,21,22</sup> Compared with strains which do not result in systemic infection, DGI strains are more resistant to complement mediated killing by normal human serum<sup>23,24</sup> but more sensitive to penicillin.<sup>25</sup> The serum resistance is, however, highest in those strains associated with a purulent arthritis which also stimulate a greater level of bacteriocidal activity in serum. This suggests that variations in the clinical presentation of DGI may reflect infection with different subtypes of *N gonorrhoeae*.<sup>3</sup>

The primary mucosal infection in DGI is usually asymptomatic<sup>21,26</sup> and it is also rare for infection to spread locally producing epididymitis or pelvic inflammatory disease.<sup>14</sup> This may be the result of impaired chemotaxis<sup>27</sup> and the presence of "blocking antibodies" directed against Protein IA, which reduce complement activation,<sup>28,29</sup> thus leading to less mucosal inflammation and a greater opportunity for haematogenous spread. Other phenotypic characteristics associated with DGI such as increased susceptibility to vancomycin (used in some gonococcal culture media) and sodium polyanethanesulphonate (used in some blood culture media) may lead to difficulties in confirming the diagnosis due to false negative results on culture.<sup>30</sup>

Strains of *N gonorrhoeae* associated with DGI tend to be highly penicillin sensitive but systemic infection with both PPNG and CMRNG have been described<sup>31-34</sup> and the incidence of penicillin resistance in DGI reflects that seen for mucosal disease for a given area.<sup>18</sup>

**How does DGI present and what treatment is most appropriate?***Clinical features*

Despite changes in the incidence of gonorrhoea, gonococcal phenotype and the demographics of infected patients the clinical features of DGI have not altered over the past

Department of  
Genitourinary  
Medicine, Edinburgh  
Royal Infirmary,  
Edinburgh EH3 9YW,  
UK  
J D C Ross

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decade.<sup>18</sup> Systemic infection with *N gonorrhoeae* generally produces a fairly mild systemic illness with the fever rarely reaching 39°C. Asymmetric polyarthralgia, which may be migratory, is the commonest presenting symptom occurring in two-thirds of cases and a further quarter of patients have a monoarthralgia.<sup>3 17 18 35</sup> The majority of individuals do not have genitourinary symptoms from the primary site of infection and may therefore present to other specialities such as dermatology or rheumatology.<sup>3 14 35</sup> The other two classical features of infection are a skin rash and tenosynovitis and some authors have suggested that an initial bacteraemic stage, associated with fever, skin rashes and tenosynovitis, is followed by localisation of the infection within the joints.<sup>14</sup> Attractive though this theory is, both the skin rash/tenosynovitis and the arthritis stages frequently co-exist<sup>36 37</sup> and the length of history in both groups is similar.<sup>3</sup> Therefore it may be more helpful in describing the clinical features of DGI to subdivide the condition according to the presence or absence of a purulent arthritis, which also has diagnostic and prognostic implications.

Around 60% of patients present without a detectable synovial effusion and over 90% of these will have a skin rash and/or tenosynovitis often in conjunction with a non-suppurative arthritis.<sup>3</sup> It is necessary to examine carefully for the rash since although only a quarter of patients will complain of skin lesions<sup>12 17</sup> the majority have a maculopapular, pustular, necrotic or vesicular rash when examined. Typically the rash occurs below the neck involving the torso, limbs, palms and soles but sparing the scalp, face and mouth.<sup>3 12</sup> Infrequently haemorrhagic skin lesions, erythema nodosum, urticaria and erythema multiforme have been described. The skin lesions are often seen in various stages of development and typically resolve over 4 to 5 days without residual scarring. The discomfort associated with tenosynovitis typically occurs in the hands and fingers but the tendons around the small and large joints of the lower limbs can also be affected.<sup>4 37</sup> Distinguishing a suppurative from non-suppurative effusion may be difficult and often requires a diagnostic tap of the affected joint.

The second group of patients present with a suppurative joint effusion typically containing 30 000 to 80 000 wbc/ $\mu$ l<sup>12</sup> and less commonly have skin lesions (40%) or tenosynovitis (20%). The knee is the most commonly affected joint with the upper limb joints and the hip less frequently involved.<sup>1 4 35</sup>

### Diagnosis

Unlike other infective arthropathies,<sup>38</sup> DGI is often associated with sterile cultures from blood and synovial fluid and the diagnosis may have to be made on the basis of the clinical features in association with positive mucosal cultures. The white cell count is seldom greater than 20 000/ $\mu$ l but the ESR is over 50 mm/h in around half the cases and anaemia and elevated transaminases are also common.<sup>3 37</sup> Blood cultures detect *N gonorrhoeae* in

a third of cases<sup>14 37</sup> and synovial fluid cultures are positive in around half the patients with a purulent effusion.<sup>3 14 37</sup> Interestingly a positive synovial fluid culture is invariably associated with negative blood cultures.<sup>3 17 35 37 39</sup> Typically cervical cultures are positive in around 90% of women, urethral cultures in 50% of men, pharyngeal cultures in 20% and rectal cultures in 15%.<sup>3 37 40</sup> but cultures from skin detect infection in under 5% of cases.<sup>3 14 19 41 42</sup> Skin biopsy followed by culture may lead to a greater diagnostic yield but is not recommended for routine clinical use.<sup>43</sup> Some authors have suggested that pharyngeal infections, by nature of their lack of symptoms, may be more likely to cause DGI<sup>44</sup> but there is little objective evidence to support this. Non viable gonococcal material can be detected in joints and skin using electron microscopy and polymerase chain reaction<sup>36 45 46</sup> in some, but not all, patients who have negative cultures suggesting that some of the clinical features are immune mediated or possibly hypersensitivity phenomena.

### Treatment

Despite low isolation rates of gonococci suggesting that direct invasion is not always the primary pathogenic mechanism, DGI is characterised by a rapid response to antibiotic therapy with complete recovery generally occurring within a few days.<sup>3 18 47</sup> In this respect it is similar to other "immune mediated" infections such as infective endocarditis. A variety of antibiotic regimes have been recommended in the past including IV amoxycillin, oral amoxycillin and oral erythromycin usually completing a 1–2 week course.<sup>48</sup> The increasing prevalence of antibiotic resistance has, however, necessitated a change in antibiotic policy.

The dose of penicillin required to treat uncomplicated gonorrhoea increased steadily between 1948 and 1972<sup>49</sup> with penicillinase producing bacteria (PPNG) identified in 1976<sup>50 51</sup> and chromosomally mediated resistance (CMRNG) in 1983.<sup>52</sup> It is therefore prudent now to include cover for penicillin resistant isolates until the sensitivities of the organism are known, for example using cefotaxime or ceftriaxone.

### Complications

Purulent joint effusions almost never result in permanent damage and, although repeated aspiration may be necessary, intra-articular antibiotics are not indicated.<sup>12</sup> Patients with a synovial effusion spend an average of 8 days in hospital compared with 4 days for those in the skin rash/tenosynovitis group and an elevated ESR on admission is also associated with a prolonged admission.<sup>3 18 53</sup>

Although involvement of the meninges, heart valves and bone have been reported these remain rare with 1–3% of patients with DGI progressing to endocarditis, most commonly affecting the aortic valve<sup>14 54 55</sup>—the last reported case of gonococcal endocarditis was however over 50 years ago. In gonococcal meningitis the patient generally has features

typical of meningism but the other features of DGI are absent.<sup>56 57</sup>

### What else can cause a similar clinical picture?

The differential diagnosis of the asymmetric arthritis of DGI includes an infective arthritis, Reiter's syndrome and rheumatic fever. Infective arthritis usually occurs in the very old, very young or immunocompromised and is commoner in men, that differentiates it from DGI which most commonly affects young sexually active women. Infective arthritis also presents as a non migratory monoarthritis and skin rashes are uncommon. In Reiter's syndrome the arthralgia is also non migratory often being confined to the lower limbs and associated with conjunctivitis and other mucosal lesions not seen in DGI. Fever is uncommon in Reiter's syndrome and unlike DGI there is a male predominance and an HLA B27 association and hyperkeratotic skin lesions are common. Rheumatic fever remains extremely uncommon in the developed world and is associated with a high fever, more marked systemic illness and a typical rash.

The skin lesions of DGI can appear identical to those of meningococcal septicaemia but such patients generally have a more acute systemic illness usually associated with symptoms and signs of meningitis.

### How does *N. gonorrhoeae* cause DGI?

The inability to detect viable organisms from synovial fluid, blood or skin in a significant number of patients suggests that the pathogenesis of DGI is not always related to direct bacterial invasion of tissue. It seems likely that an immune process is also implicated possibly with the deposition of antibody-antigen immune complexes in tissue and/or cross reaction between gonococcal and host tissue antigens. The ability to detect gonococcal DNA in some culture negative joints<sup>46</sup> and the presence of immune complexes from culture negative skin lesions and synovium<sup>41 58 59</sup> supports an immune mechanism, as does the occasional occurrence of immune mediated skin lesions such as erythema nodosum and erythema multiforme.<sup>41</sup> In animal models an identical suppurative arthritis can be induced by the intra-articular injection of killed gonococci, gonococcal lipopolysaccharide or live gonococci and even after live bacteria have been injected into the joint viable organisms are undetectable within a few hours.<sup>60</sup> However, treatment with antibiotics, although producing a good clinical response, does not appear to reduce the level of circulating immune complexes.<sup>59</sup>

Complement activation has a central role in controlling the spread of *N. gonorrhoeae* by acting as a chemoattractant for polymorphs,<sup>61</sup> opsonising bacteria<sup>62 63</sup> and via the antibody-complement mediated bacteriocidal activity of serum.<sup>64 65</sup> Complement deficiencies are associated with recurrent DGI<sup>66-68</sup> but screening is only indicated in patients presenting with a

second or subsequent episode, given the rarity of such deficiencies.

### Conclusions

The precise mechanism by which *N. gonorrhoeae* causes DGI remains unclear as are the reasons why infection becomes systemic in a small number of individuals. Even using sensitive techniques a clinical diagnosis can still not always be confirmed bacteriologically and empirical therapy with antibiotics to cover penicillin resistant organisms may be necessary. DGI remains an important option in the differential diagnosis of arthritis or pyrexia of unknown origin in young adults.

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